

DESCRIPTION

NONAQUEOUS PRESSURE-SENSITIVE ADHESIVE FOR MEDICINAL TAPE
PREPARATION FOR PERCUTANEOUS ABSORPTION, MEDICINAL TAPE
5 PREPARATION FOR PERCUTANEOUS ABSORPTION, AND PROCESS FOR
PRODUCING THE SAME

Technical Field

[0001]

10 The present invention relates to a nonaqueous pressure-
sensitive adhesive for a medicinal tape preparation for
percutaneous absorption, comprising a copolymer obtained by
copolymerization of a (meth)acrylic monomer having an
acetoacetyl group in the molecule and one or more monomers
15 selected from among other (meth)acrylic monomers with no
acetoacetyl group and copolymerizable vinyl monomers, in a
nonaqueous solvent, as well as to a medicinal tape
preparation for percutaneous absorption produced by coating
a nonaqueous pressure-sensitive adhesive onto the top side
20 of a support or release film, together with a drug and
plasticizer, and heating to dryness to form a pressure-
sensitive adhesive layer, and then further laminating a
release film or support over the pressure-sensitive adhesive
layer, and to a process for producing the same. The
25 medicinal tape preparation for percutaneous absorption
according to the invention is a highly stable tape
preparation for percutaneous absorption which exhibits

excellent drug release from the preparation and excellent drug skin permeability, with low skin irritation.

Background Art

5 [0002]

Paints, coatings and pressure-sensitive adhesives are known wherein copolymers obtained by copolymerization of acetoacetoxyalkyl methacrylates and other monomers are crosslinked with crosslinking agents such as polyamine compounds or isocyanate compounds. (See, for example, Patent document 1 and Patent document 2). However, no patent document or non-patent document can be found which describes the use of a nonaqueous pressure-sensitive adhesive comprising a copolymer obtained by copolymerization of a (meth)acrylic monomer having an acetoacetyl group, and one or more monomers selected from among other (meth)acrylic monomers and copolymerizable vinyl monomers, as the pressure-sensitive adhesive used in a medicinal tape preparation for percutaneous absorption.

20 [0003]

Tape preparations for percutaneous absorption have been known which comprise a drug and plasticizer in a pressure-sensitive adhesive layer, wherein a ketone group-containing pressure-sensitive adhesive is substantially crosslinked with a polyamine crosslinking agent. (See, for example, Patent document 3). However, no description is found of a tape preparation for percutaneous absorption having a

pressure-sensitive adhesive comprising a copolymer with an acetoacetyl group.

[0004]

There have also been known preparations for percutaneous absorption which contain an isosorbide dinitrate coronary vasodilator and a fatty acid ester in a crosslinked pressure-sensitive adhesive comprising an acrylic copolymer composed of an acrylic acid alkyl ester and a functional monomer as essential components. (See, for example, Patent document 4). However, this preparation for percutaneous absorption employs a crosslinking agent, and it is stated that without a crosslinking agent the pressure-sensitive adhesive layer lacks cohesive strength and cannot be used in a preparation for percutaneous absorption. In addition, Patent documents 3 and 4 do not provide examples of tape preparations for percutaneous absorption with pressure-sensitive adhesives comprising copolymers with acetoacetyl groups.

[0005]

Patent document 1: Japanese Unexamined Patent Publication HEI No. 6-108033

Patent document 2: Japanese Unexamined Patent Publication HEI No. 7-238203

Patent document 3: Japanese Unexamined Patent Publication No. 2002-535475

Patent document 4: Japanese Unexamined Patent Publication HEI No. 8-81369

Disclosure of the Invention

Problems to be Solved by the Invention

[0006]

5 It is an object of the present invention to provide a medicinal tape preparation for percutaneous absorption having a drug-containing pressure-sensitive adhesive layer formed on a support and a release liner laminated thereover, wherein a large amount of a lipophilic oily substance can be
10 included in the pressure-sensitive adhesive layer and the preparation has excellent adhesion, cohesive strength and stability, as well as a nonaqueous pressure-sensitive adhesive for the preparation.

[0007]

15 The pressure-sensitive adhesive layer of the medicinal tape preparation for percutaneous absorption may also contain, in addition to a drug, also a solvent for dissolution of the drug, a percutaneous absorption accelerator to accelerate the percutaneous absorption rate
20 of the drug, a plasticizer for improved plasticity of the pressure-sensitive adhesive or a tackifier for improved adhesive strength, and in some cases it may be necessary to include such components in significant amounts. The drug-dissolving solvent, percutaneous absorption accelerator,
25 plasticizer and tackifier included with the drug in the pressure-sensitive adhesive layer will usually be lipophilic oily substances.

[0008]

Problems have been encountered with conventional medicinal tape preparations for percutaneous absorption employing a non-crosslinked pressure-sensitive adhesive, in that it has not been possible to hold large amounts of oily substances, or when large amounts of oily substances are contained it has not been possible to form tape preparations and the oily substances have separated from the pressure-sensitive adhesive layers after formation of the preparations, and therefore the amounts of oily substances in pressure-sensitive adhesive layers have been limited.

[0009]

In order to overcome these problems, there have also been studied tape preparations wherein a pressure-sensitive adhesive obtained by polymerizing a functional group-containing monomer is crosslinked with a crosslinking agent such as a polyamine compound, isocyanate compound or polyvalent metal chelate compound. However, such crosslinking agents are often toxic compounds or they have undesirable effects on certain drugs, while restrictions are necessary on their use or the amounts of their use.

[0010]

Self-crosslinking pressure-sensitive adhesives employing no crosslinking agents are known, such as pressure-sensitive adhesives comprising N-methylolacrylamide as a constituent monomer, but such adhesives are not preferred for medicinal pressure-sensitive adhesive tapes

due to gradually release of the harmful substance
formaldehyde.

[0011]

There are also known copolymers comprising acetoacetyl
5 group-containing monomers as constituent monomers, for use
as paints, coating agents and adhesives, but all such
compounds are crosslinked using crosslinking agents such as
polyamine derivatives, isocyanate compounds and polyvalent
metal chelate compounds, and their use in medicinal tape
10 preparations for percutaneous absorption is not known. In
addition, these crosslinking agents are associated with such
problems as toxicity and unsuitability for certain types of
drugs.

Means for Solving the Problems

15 [0012]

As a result of much research conducted with the aim of
solving the problems described above, the present inventors
discovered that it is possible to hold large amounts of oily
substances such as plasticizers by using a nonaqueous
20 pressure-sensitive adhesive comprising a copolymer obtained
by copolymerization of a (meth)acrylic monomer having an
acetoacetyl group in the molecule and one or more monomers
selected from among other (meth)acrylic monomers with no
acetoacetyl group and copolymerizable vinyl monomers, in a
25 nonaqueous solvent.

[0013]

The nonaqueous pressure-sensitive adhesive used in the

medicinal tape preparation for percutaneous absorption of the invention, comprising a copolymer obtained by copolymerization of a (meth)acrylic monomer having an acetoacetyl group and one or more vinyl monomers selected from among other (meth)acrylic monomers with no acetoacetyl group and copolymerizable vinyl monomers, in a nonaqueous solvent, undergoes self-crosslinking of the acetoacetyl groups as the solvent evaporates during the step of coating onto a support or release film together with a drug and plasticizer followed by heating to dryness, thereby forming a network structure with the oily substances such as the plasticizer held in the network structure.

[0014]

By adjusting the amount of acetoacetyl group-containing (meth)acrylic monomer in the starting material, it is possible to alter the degree of self-crosslinking of the pressure-sensitive adhesive. It was discovered that, as a result, it is possible to adjust the content of lipophilic oily substances such as plasticizers, percutaneous absorption accelerators, drug dissolving agents and the like in the pressure-sensitive adhesive layer, and that by modifying the content ratio of the pressure-sensitive adhesive and the plasticizer or percutaneous absorption accelerator it is possible to produce suitable adhesion and cohesive strength and obtain a stable tape preparation for percutaneous absorption; the present invention was completed on the basis of this discovery.

Effect of the Invention

[0015]

In the step of heat drying the nonaqueous pressure-sensitive adhesive copolymer comprising a (meth)acrylic monomer having an acetoacetyl group as a constituent monomer according to the invention, a network structure is formed by self-crosslinking of the acetoacetyl groups as the solvent evaporates, so that large amounts of oily substances such as the plasticizer can be included in the network structure. The pressure-sensitive adhesive of the invention uses no polyamine derivatives, isocyanate compounds or polyvalent metal chelate compounds as crosslinking agents, and therefore since toxicity is not a concern and the skin is not irritated, the adhesive is suitable for medical use. The medicinal tape preparation for percutaneous absorption of the invention has excellent adhesive and cohesive strength, and is highly safe with low skin irritation. Its properties of drug release and percutaneous absorption are also excellent.

Best Mode for Carrying Out the Invention

[0016]

The nonaqueous pressure-sensitive adhesive for a medicinal tape preparation for percutaneous absorption according to the invention may be obtained by copolymerization of a (meth)acrylic monomer having an

acetoacetyl group in the same molecule and one or more monomers selected from among (meth)acrylic monomers with no acetoacetyl group and copolymerizable vinyl monomers, in a nonaqueous solvent.

5 [0017]

As (meth)acrylic monomers having an acetoacetyl group there may be mentioned acetoacetoxylalkyl methacrylates or acetoacetoxylalkyl acrylates such as 2-acetoacetoxylethyl methacrylate, 2-acetoacetoxylethyl acrylate, 3-
10 acetoacetoxylpropyl methacrylate, 3-acetoacetoxylpropyl acrylate, 4-acetoacetoxylbutyl methacrylate and 4-acetoacetoxylbutyl acrylate, among which any one or more may be used, although 2-acetoacetoxylethyl methacrylate and 2-acetoacetoxylethyl acrylate are preferred.

15 [0018]

As other (meth)acrylic monomers having no acetoacetyl group there may be used any (meth)acrylic monomers having a copolymerizable double bond in the molecule, and one or more such (meth)acrylic monomers may be used. As specific
20 examples there may be mentioned one or more (meth)acrylic monomers selected from the group consisting of 2-ethylhexyl acrylate, 2-ethylhexyl methacrylate, diacetoneacrylamide, butyl acrylate, butyl methacrylate, ethyleneglycol dimethacrylate, diethyleneglycol dimethacrylate,
25 triethyleneglycol methacrylate, tetraethyleneglycol diacrylate, tetraethyleneglycol dimethacrylate, hexaethyleneglycol dimethacrylate, hexaethyleneglycol

diacrylate, methyl methacrylate, acrylamide, methacrylamide, 2-hydroxyethyl acrylate and acrylic acid, of which there are preferred one or more acrylic monomers selected from the group consisting of 2-ethylhexyl acrylate,

5 diacetoneacrylamide, butyl acrylate, tetraethyleneglycol diacrylate, tetraethyleneglycol dimethacrylate and methyl methacrylate.

[0019]

The other vinyl compound which is copolymerizable with
10 the monomer having an acetoacetyl group need only have a copolymerizable vinyl group in the molecule, and as examples there may be mentioned vinyl derivatives such as N-vinyl-2-pyrrolidone and vinyl acetate.

[0020]

15 The content of the acetoacetyl group-containing monomer in the copolymer used in the nonaqueous pressure-sensitive adhesive of the invention is preferably 1-40 wt% and more preferably 5-40 wt% with respect to the total weight of the copolymer. The proportion is preferably not smaller than 1
20 wt%, because the oily substance-holding power and the cohesive strength will be reduced, and it is preferably not greater than 40 wt% because the network structure will become too dense, reducing the holding power for the plasticizer and other components.

25 [0021]

The solvent of the nonaqueous pressure-sensitive adhesive for the medicinal tape preparation for percutaneous

absorption according to the invention may be any organic solvent which volatilizes in the heat drying step during the production process for the medicinal tape preparation for percutaneous absorption of the invention. Such a solvent
5 may be any of various organic solvents including acetic acid esters such as methyl acetate, ethyl acetate, propyl acetate and butyl acetate, aliphatic hydrocarbons such as hexane, heptane, octane and cyclohexane, aromatic hydrocarbons such as benzene, toluene and xylene, ketones such as acetone and
10 methyl ethyl ketone, and ethers such as isopropyl ether, tetrahydrofuran and dioxane, among which any may be used alone, or two or more may be used in combination.

[0022]

The nonaqueous pressure-sensitive adhesive of the
15 invention may be produced by a well-known method in the relevant technical field. A specific preferred method is dissolution of each of the monomers in an organic solvent and polymerization with a radical initiator.

[0023]

20 Alternatives include dissolution of all of the monomers in a prescribed organic solvent beforehand, nitrogen substitution, and then heating for polymerization, or successive loading of the monomer in separate amounts into the solvent for polymerization. The monomer concentration
25 in the organic solvent is preferably 10-80 wt%. The concentration is preferably not less than 10 wt% because it will be difficult to achieve a high polymerization degree,

while it is preferably not greater than 80 wt% because control of the heat of polymerization during the reaction will become difficult. The organic solvent used for the polymerization may be any single solvent selected from the group consisting of organic solvents mentioned above, or a combination of two or more thereof. Also, the same type or different types of solvents may be added successively during the polymerization.

[0024]

The radical initiator used for the invention may be a compound selected from among peroxides, azo initiators and the like, or a mixture thereof, and it is used in an amount of preferably 0.001-2.00 parts by weight and more preferably 0.005-0.1 part by weight to 100 parts by weight of the monomer.

[0025]

As specific peroxides there may be mentioned benzoyl peroxide, lauroyl peroxide, tert-butyl hydroperoxide, di(2-ethylhexyl)peroxydicarbonate and 1,1'-di-tert-butyl-peroxy-2-methylcyclohexane. As specific azo initiators there may be mentioned 2,2'-azobisisobutyronitrile, 4,4'-azobis-4-cyanovaleric acid and 2,2'-azobis(2-amidinopropane) dihydrochloride.

[0026]

The polymerization temperature may be a temperature at which the radical initiator generates a suitable level of radicals, and in most cases it is preferably 50-120°C.

[0027]

The amount of residual monomer of the nonaqueous pressure-sensitive adhesive of the invention is preferably minimized for reduced skin irritation and improved drug stability, and preferably it is no greater than 20,000 ppm with respect to the solid portion of the pressure-sensitive adhesive. In order to reduce the residual monomer, for example, additional radical initiator may be added after completion of the polymerization, or high-temperature treatment may be carried out under pressurized conditions.

[0028]

A greater molecular weight of the copolymer of the pressure-sensitive adhesive of the invention will result in inferior adhesion, while a smaller molecular weight will result in inferior cohesive strength. The molecular weight of the copolymer may be a weight-average molecular weight of between several tens of thousands to several million.

[0029]

The glass transition temperature (hereinafter also referred to as "Tg") of the copolymer of the pressure-sensitive adhesive of the invention also has a significant effect on the adhesive and cohesive strength of the pressure-sensitive adhesive, with a high Tg tending to result in a harder pressure-sensitive adhesive and a low Tg tending to results in a softer one, and therefore the Tg of the copolymer is preferably in the range of -60°C to -5°C. The range is more preferably between -50°C and -10°C. If it

is below -60°C, the cohesive strength of the pressure-sensitive adhesive will tend to be too weak when the plasticizer is added, while a Tg of higher than -5°C will tend to result in poor adhesive strength even with addition
5 of a large amount of plasticizer.

[0030]

The glass transition temperature can generally be determined by measurement with a DSC apparatus or measurement of the viscoelasticity. It can also be derived
10 by calculation using the following formula 1, as the glass transition temperature of the homopolymer.

$$\frac{100}{T_g} = \sum \frac{W_i}{T_{gi}} \quad (1)$$

(wherein W_i represents the weight fraction (%) of the monomer of component "i", and T_{gi} represents the glass
15 transition temperature (°K) of the homopolymer of component "i".)

[0031]

The plasticizer included in the pressure-sensitive adhesive layer of the medicinal tape preparation for
20 percutaneous absorption of the invention may be an oily substance with a high boiling point in most cases. For example, there may be used fatty acid ester derivatives such as isopropyl myristate, diethyl sebacate, diisopropyl adipate, ethyl oleate, isopropyl palmitate, ethyl laurate,
25 octyl palmitate, isotridecyl myristate and medium-chain fatty acid triglycerides; higher alcohol derivatives such as

hexyldecanol and octyldodecanol; polyalkylene glycols such as polyethylene glycol and polypropylene glycol; and fats and oils such as olive oil, castor oil and the like. These may be used alone or in mixtures of two or more, but
5 isopropyl myristate and isopropyl palmitate are most preferred because they function as plasticizers for the pressure-sensitive while also accelerating diffusion of the drug in the tape preparation and promoting skin permeability of the drug. The plasticizer content is preferably no
10 greater than 50 wt% and more preferably 10-40 wt% with respect to the total weight of the pressure-sensitive adhesive layer. The plasticizer content is preferably not greater than 50 wt% because such an amount cannot be held in the pressure-sensitive adhesive layer, and the oily
15 substances will tend to bleed from the pressure-sensitive adhesive layer.

[0032]

The pressure-sensitive adhesive in the pressure-sensitive adhesive layer of the medicinal tape preparation
20 for percutaneous absorption of the invention exhibits suitable adhesive strength even alone if it contains a percutaneous absorbing drug and a plasticizer in addition to the nonaqueous pressure-sensitive adhesive, but if even stronger adhesive strength is desired, a tackifier may be
25 included in the pressure-sensitive adhesive layer to increase the adhesive strength, and examples of tackifiers that are suitable for use include alicyclic saturated

hydrocarbon resins and rosin ester derivatives. Alicyclic saturated hydrocarbon resins include ALCON P-100 (trade name of Arakawa Chemical Industries Co., Ltd.) while rosin ester derivatives include ESTERGUM H (trade name of Arakawa Chemical Industries Co., Ltd.), and any one or mixtures of two or more may be used.

[0033]

There are no particular restrictions on drugs to be formulated in the tape preparation for percutaneous absorption of the invention, and they may be selected to conform to the purpose of treatment; examples of suitable drugs include steroid hormones, non-steroidal anti-inflammatory drugs, tranquilizers, anti-hypertensive agents, ischemic heart disease drugs, anti-histamines, antiasthmatic drugs, anti-Parkinson drugs, cerebral circulation improvers, antiemetics, anti-depressants, anti-dementia drugs, Sjogren's syndrome treatments, anti-arrhythmia drugs, anticoagulants, gout suppressants, antifungal agents, narcotic analgesics, beta blockers, $\beta 1$ agonists, $\beta 2$ agonists, antitumor agents, diuretics, antithrombotic agents, histamine H1 receptor antagonists, histamine H2 receptor antagonists, anti-allergic agents, serotonin receptor antagonists, anti-hypercholesteremic agents and smoking cessation aids, and any percutaneously absorbed drugs may be used which do not reside on the skin surface but penetrate to the subcutaneous layer or into the blood to exhibit a local or systemic effect. Two or more of such drugs may

also be used together if necessary. Also, the contents of the drugs may be appropriately set depending on the type of drug, its effect and the purpose of administration.

[0034]

5 If necessary, the pressure-sensitive adhesive layer of the tape preparation for percutaneous absorption of the invention may also include, in addition to the aforementioned drug, pressure-sensitive adhesive and plasticizer, also a drug solubilizer, percutaneous
10 absorption accelerator and other excipients.

[0035]

 A drug solubilizer is a drug-dissolving solvent, and any solvent which is not skin-irritating may be used. Specifically, there may be used lower alcohols such as
15 ethanol, propanol and isopropanol, medium alcohols such as hexanol and octanol, polyhydric alcohols such as glycerin, ethylene glycol and diethyleneglycol, fatty acid esters, polyvinyl alcohols, N-methylpyrrolidone, crotamiton and the like, any of which may be used alone or in combinations of
20 two or more as drug-dissolving agents, although there is no limitation to these.

[0036]

 As drug percutaneous absorption accelerators there may be used any which are commonly utilized in tape preparations
25 for percutaneous absorption, including fatty acid esters such as isopropyl myristate, isopropyl palmitate and diisopropyl adipate, fatty acid polyhydric alcohol esters

such as caprylic monoglyceride, caprylic triglyceride and sorbitan fatty acid esters, and terpenes such as 1-menthol, peppermint oil and limonene.

[0037]

5 Examples of excipients include silicon compounds such as silicic anhydride and light silicic anhydride, cellulose derivatives such as ethyl cellulose, methyl cellulose, carboxymethylcellulose sodium, hydroxypropyl cellulose and hydroxypropylmethyl cellulose, water-soluble polymers such
10 as polyvinyl alcohol, antioxidants such as dibutylhydroxytoluene and powders such as kaolin and titanium oxide, as well as aromatics and coloring agents, and these may be added in medically acceptable ranges.

[0038]

15 There are no particular restrictions on the support for the tape preparation for percutaneous absorption of the invention, and there may be used stretchable or non-stretchable woven or nonwoven fabric or knit textiles made of polyethylene, polypropylene, polyester or the like,
20 plastic films made of polyethylene, polypropylene, polyester, ethylene-vinyl acetate copolymer, vinyl chloride or the like, or foam films made of polyurethane or the like, either alone or in laminated combinations, depending on the purpose of use.

25 [0039]

 The release liner on the tape preparation for percutaneous absorption of the invention serves to protect

the pressure-sensitive adhesive layer during storage, and there may be used polyester, polyethylene, polypropylene, ethylene-vinyl acetate copolymer resin, polyurethane, a metal foil thin-film, a film having a laminated structure comprising a combination of such materials, a film which has been silicon-treated on the surface to be attached to the pressure-sensitive adhesive layer, or a film having a metal such as aluminum vapor-deposited on the surface. In addition, the release liner may be provided with a continuous or non-continuous straight or curved notch for easier release.

[0040]

The tape preparation for percutaneous absorption of the invention may be produced by coating the surface of the release liner with a solution containing the drug, plasticizer and if necessary a drug-dissolving agent or percutaneous absorption accelerator, with the pressure-sensitive adhesive, and then heating to dryness at a temperature of 40-150°C to form a pressure-sensitive adhesive layer, subsequently laminating a support on the surface of the pressure-sensitive adhesive layer opposite the side on which the release liner is attached, and cutting it to an appropriate size. When a non-water-permeable support is used as the support, a pressure-sensitive adhesive solution containing the drug, plasticizer, etc. may be applied onto the support and heated to dryness, and then the release liner laminated thereon. The temperature for

heating to dryness may be a temperature above the volatilization temperature of the solvent. The temperature is preferably not too low because the solvent will not completely volatilize, and it is preferably not above 150°C because an adverse effect may be produced on the drug, plasticizer and percutaneous absorption accelerator.

Examples

[0041]

10 The nonaqueous pressure-sensitive adhesive for the medicinal tape preparation for percutaneous absorption of the invention and the medicinal tape preparation for percutaneous absorption will now be further explained through the following examples, with the understanding that
15 the invention is in no way limited to these examples.

[0042]

Example 1 Production of nonaqueous pressure-sensitive adhesive 1

20 After charging 157.5 g of 2-ethylhexyl acrylate (hereinafter abbreviated as 2EHA), 35 g of 2-acetoacetoxyethyl methacrylate (hereinafter abbreviated as AAEM), 80.5 g of diacetoneacrylamide (hereinafter abbreviated as DAAM) and 76 g of methyl methacrylate (hereinafter abbreviated as MMA) in a 2-liter four-necked
25 flask equipped with a Dimroth condenser, thermometer, nitrogen gas blow-in tube and stirrer, 525 g of ethyl acetate was added as a solvent and the mixture was dissolved

to uniformity. The temperature was raised to 75°C while blowing in nitrogen gas at flow rate of 100 ml/min. After holding at 75°C for 30 minutes, a solution of 0.21 g of benzoyl peroxide as an initiator in 5 g of ethyl acetate was added, and the external temperature was set to 85°C. Subsequently, 300 g of toluene was loaded in portions of 100 g at a time at 3, 5 and 7 hours after adding the initiator. During the polymerization, nitrogen gas was continuously blown in at a flow rate of 100 ml/min.

At 12 hours after the final toluene loading, 0.35 g of benzoyl peroxide was loaded as an additional catalyst, and then heat treatment for 12 hours at an external temperature of 95°C was followed by cooling to obtain nonaqueous pressure-sensitive 1.

[0043]

(Physical properties of solution of nonaqueous pressure-sensitive adhesive 1)

Solution viscosity (measured with Brookfield viscometer):
30,000 mPa·s

Solid portion (150°C x 1 hour treatment): 28.5%

Residual monomers: 300 ppm 2EHA, 20 ppm AAEM, 1000 ppm DAAM,
150 ppm MMA (measured by HPLC)

[0044]

Example 2 Production of nonaqueous pressure-sensitive adhesive 2

A monomer solution was prepared by uniformly pre-dissolving 78.8 g of 2EHA, 78.8 g of n-butyl acrylate

(hereinafter abbreviated as BA), 105 g of AAEM, 87.5 g of MMA and 1.05 g of diethyleneglycol dimethacrylate (hereinafter abbreviated as DEGMA). After adding 100 g of the monomer solution in a 2-liter four-necked flask equipped with a Dimroth condenser, thermometer, nitrogen gas blow-in tube and stirrer, 350 g of ethyl acetate was added as a solvent. The temperature was raised to 75°C while blowing in nitrogen gas at flow rate of 100 ml/min, and after holding at 75°C for 30 minutes, a solution of 0.35 g of benzoyl peroxide as an initiator in 5 g of ethyl acetate was added, and the external temperature was set to 85°C. Upon confirming reflux of the solvent, the remaining monomer solution was loaded continuously for 3 hours. Next, one hour after the initial continuous loading of the monomer solution, 500 g of ethyl acetate was continuously loaded for 3 hours. After continuing to stir for 12 hours after loading the ethyl acetate, 0.5 g of benzoyl peroxide was loaded as additional catalyst and then heat treatment for 12 hours was followed by cooling to obtain nonaqueous pressure-sensitive 2. During the polymerization, nitrogen gas was continuously blown in at a flow rate of 100 ml/min.

[0045]

(Physical properties of solution of nonaqueous pressure-sensitive adhesive 2)

Solution viscosity (measured with Brookfield viscometer):
25,000 mPa·s
Solid portion (150°C x 1 hour treatment): 27.5%

Residual monomers: 1000 ppm 2EHA, 200 ppm BA, 100 ppm AAEM,
250 ppm MMA, DEGMA below detection limit (measured by HPLC)
[0046]

Nonaqueous pressure-sensitive adhesives 3-10 for
5 Examples 3-10 shown in Table 1 were produced by the method
described in Example 2.

[0047]

Comparative Example 1 Production of comparison pressure-
sensitive adhesive 1

10 Polymerization and synthesis were conducted by the same
method as for pressure-sensitive adhesive 1 of Example 1
using a monomer composition of 90 g 2EHA, 90 g BA, 80.5 g
DAAM, 87.5 g MMA and 1.0 g DEGMA, to produce comparison
pressure-sensitive adhesive 1.

15 [0048]

(Physical properties of solution of comparison pressure-
sensitive adhesive 1)

Solution viscosity (measured with Brookfield viscometer):
38,000 mPa·s

20 Solid portion (150°C x 1 hour treatment): 28.5%

Residual monomers: 300 ppm 2EHA, 200 ppm BA, 1500 ppm DAAM,
100 ppm MMA, DEGMA below detection limit (measured by HPLC)
[0049]

Comparative Example 2 (Preparation of comparison pressure-
25 sensitive adhesive 2)

Polymerization and synthesis were conducted by the same
method as in Example 2 using a monomer composition of 130 g

2EHA, 130 g BA and 90 g MMA, to produce comparison pressure-sensitive adhesive 2.

[0050]

(Physical properties of solution of comparison pressure-sensitive adhesive 2)

Solution viscosity (measured with Brookfield viscometer):

28,000 mPa·s

Solid portion (150°C x 1 hour treatment): 27.5%

Residual monomers: 500 ppm 2EHA, 300 ppm BA, 150 ppm MMA

10 (measured by HPLC)

[0051]

The monomer compositions, solvents and calculated T_g values for the nonaqueous pressure-sensitive adhesives of Examples 1-10 and Comparative Examples 1 and 2 are shown in

15 Table 1.

[0052]

Table 1 Nonaqueous pressure-sensitive adhesives

Example	Monomer							Solvent	Calculated Tg value
	AAEM	DAAM	MMA	2EHA	BA	DEGMA	TEGMA		
1	10.0	23.1	21.8	45.1				EtOAc, toluene	-12.3
2	29.9		24.9	22.5	22.5	0.2		EtOAc, toluene	-15.0
3	0.1		28.9	35.4	35.4	0.2		EtOAc, toluene	-32.2
4	1.0		29.0	34.8	35.0	0.2		EtOAc, toluene	-31.6
5	5.0		25.0	34.8	35.0	0.2		EtOAc, toluene	-33.7
6	10.0		10.0	40.0	39.8	0.2		EtOAc, toluene	-47.6
7	10.0	22.9	21.8	45.0			0.3	EtOAc, toluene	-12.0
8	20.0		20.0	29.8	30.0	0.2		EtOAc, toluene	-29.3
9	30.0		25.0	22.4	22.4	0.2		EtOAc, toluene	-15.0
10	40.0		19.9	20.0	19.9	0.2		EtOAc, toluene	-27.5
Comp. Ex.1	0	23.1	25.1	25.8	25.8	0.2		EtOAc, toluene	-9.2
Comp. Ex.2	0		25.8	37.1	37.1			EtOAc, toluene	-36

AAEM: 2-acetoacetoxyethyl methacrylate; DAAM: diacetoneacrylamide; MMA: methyl methacrylate; 2EHA: 2-ethylhexyl acrylate; BA: n-butyl acrylate; DEGMA: diethyleneglycol dimethacrylate; TEGMA: tetraethyleneglycol dimethacrylate; EtOAc: ethyl acetate

The values in the monomer columns are the weight percentages of each monomer with respect to 100 as the total dry copolymer weight.

[0053]

Test Example 1

The nonaqueous pressure-sensitive adhesives 1-10 of the invention and the comparison pressure-sensitive adhesives 1 and 2 shown in Table 1, and the commercially available acrylic solvent-type (nonaqueous) pressure-sensitive adhesive S-3403 (ARONTACK S-3403, trade name of Toa Gosei Co., Ltd.) were used for coating and drying onto a support to produce tapes 2-1 to 2-21 and comparison tapes 3-5, and the compatibility of the pressure-sensitive adhesives and oily substances, the adhesive and cohesive strengths of the pressure-sensitive adhesives were evaluated.

[0054]

1) Tape production methods

15 Production of tape 2-1

A 38.69 g portion of pressure-sensitive adhesive 1 was placed in a screw-cap bottle and stirred for more than an hour in the bottle. A coating tester (LTE-S, Wener Mathis AG) was used for coating and drying of the solution onto a support (polyester film) to a dried coating weight of 70 mg/10 cm², and then a liner (silicon-treated polyester film) was used to cover it with the silicon side contacting the pressure-sensitive to obtain tape 2-1.

[0055]

25 Production of tape 2-2

A 38.69 g portion of pressure-sensitive adhesive 1, and then 1.2 g of isopropyl myristate (IPM), were placed in a

screw-cap bottle and stirred for more than an hour in the bottle. A coating tester (LTE-S, Wener Mathis AG) was used for coating and drying of the solution onto a support (polyester film) to a dried coating weight of 70 mg/10 cm², and then a liner (silicon-treated polyester film) was used to cover it with the silicon side contacting the pressure-sensitive to obtain tape 2-2.

Pressure-sensitive adhesives and corresponding plasticizers were used in the same method as the production method of tape 2-2 to produce tapes 2-3 to 2-21 and comparison tape 3-5.

[0056]

2) Evaluation of compatibility between pressure-sensitive adhesives and oily substances

The preparation liners were released and an optical microscope was used to observe the condition of liquid substance adhering to the liner surface.

Evaluation:

O: No liquid substance on the liner surface

×: Liquid substance on the liner surface

[0057]

3) Evaluation of tape adhesive strength

After releasing the liner of the preparation, the pressure-sensitive adhesive side was touched with a finger and evaluated based on the following evaluation scale.

O: (excellent) Adhesive strength comparable to MOHRUS TAPE (trade name of Hisamitsu Pharmaceutical) and YAKUBAN

(trade name of Mikasa Seiyaku) which employ styrene-isoprene-styrene copolymer.

Δ: (good) Adhesive strength comparable to SERASTAR (trade name of Yamanouchi Pharmaceutical) and FALZY (trade name of Sawai Pharmaceutical) which employ natural rubber latex.

×: (poor) Adhesive strength below that of commercial products.

-: Evaluation impossible due to significantly low cohesive strength (semi-solid state).

[0058]

4) Evaluation of tape cohesive strength (hardness)

After releasing the liner of the tape, the pressure-sensitive adhesive side was touched with a finger and evaluated based on the following evaluation scale.

Evaluation:

O: (excellent) Cohesive strength comparable to SERASTAR (trade name of Yamanouchi Pharmaceutical) and FALZY (trade name of Sawai Pharmaceutical) which employ natural rubber latex.

Δ: (good) Cohesive strength comparable to MOHRUS TAPE (trade name of Hisamitsu Pharmaceutical) and YAKUBAN (trade name of Mikasa Seiyaku) which employ styrene-isoprene-styrene copolymer.

×: (poor) Cohesive strength below that of commercial products.

[0059]

Tapes 2-1 to 2-21 and comparison tape 3-5 were used for evaluation of the compatibility of the pressure-sensitive adhesives and oily substances, the adhesive and cohesive strengths, giving the results shown in Table 2. The comparison tapes 3 and 4, and comparison tape 5 which employed a commercially available acrylic pressure-sensitive adhesive, all exhibited inadequate adhesive and cohesive strength, while tapes 2-1 to 2-21 which were prepared using nonaqueous pressure-sensitive adhesives of the invention exhibited adequate adhesive and cohesive strength.

[0060]

Table 2 Compatibilities, adhesive strengths and cohesive strengths of nonaqueous pressure-sensitive adhesive tapes

Tape No.	Monomer				Solvent			Plasticizer	Compati- bility	Adhesive strength	Cohesive strength
	AAEM	DAAM	MMA	2EHA	BA	DEGMA	TEGMA				
2-1	10.0	23.1	21.8	45.1				EtoAc, toluene	o	o	o
2-2	10.0	23.1	21.8	45.1				EtoAc, toluene	o	o	o
2-3	10.0	23.1	21.8	45.1				EtoAc, toluene	o	o	o
2-4	10.0	23.1	21.8	45.1				EtoAc, toluene	o	o	o
2-5	10.0	23.1	21.8	45.1				EtoAc, toluene	o	o	o
2-6	10.0	23.1	21.8	45.1				EtoAc, toluene	o	o	o
2-7	10.0	23.1	21.8	45.1				EtoAc, toluene	o	o	o
2-8	10.0	23.1	21.8	45.1				EtoAc, toluene	o	o	o
2-9	10.0	23.1	21.8	45.1				EtoAc, toluene	o	o	o
2-10	10.0	23.1	21.8	45.1				EtoAc, toluene	o	o	o
2-11	10.0	23.1	21.8	45.1				EtoAc, toluene	o	o	o
2-12	10.0	23.1	21.8	45.1				EtoAc, toluene	o	o	o
2-13	29.9		24.9	22.5	22.5	0.2		EtoAc, toluene	o	o	o
2-14	0.1		28.9	35.4	35.4	0.2		EtoAc, toluene	o	o	o
2-15	1.0		29.0	34.8	35.0	0.2		EtoAc, toluene	o	o	o
2-16	5.0		25.0	34.8	35.0	0.2		EtoAc, toluene	o	o	o
2-17	10.0		10.0	40.0	39.8	0.2		EtoAc, toluene	o	o	o
2-18	10.0	22.9	21.8	45.0			0.3	EtoAc, toluene	o	o	o
2-19	20.0		20.0	29.8	30.0	0.2		EtoAc, toluene	o	o	o
2-20	30.0		25.0	22.4	22.4	0.2		EtoAc, toluene	o	o	o
2-21	40.0		19.9	20.0	19.9	0.2		EtoAc, toluene	o	o	o
Comp. Ex. 3	0	23.1	25.1	25.8	25.8	0.2		EtoAc, toluene	o	-	x
Comp. Ex. 4	0		25.8	37.1	37.1			EtoAc, toluene	o	-	x
Comp. Ex. 5	Acrylic solvent-type pressure-sensitive adhesive: S-3403 (ARONTACK S-3403 Toa Gosei Co., Ltd.)							IPM 20	o	-	x

AAEM: 2-acetoacetoxethyl methacrylate; DAAM: diacetoneacrylamide; MMA: methyl methacrylate; 2EHA: 2-ethylhexyl acrylate; BA: n-butyl acrylate; DEGMA: diethyleneglycol dimethacrylate; TEGMA: tetraethyleneglycol dimethacrylate; EtoAc: ethyl acetate; IPM: isopropyl myristate; IPP: isopropyl palmitate; HD: hexyldecanol; DES: diethyl sebacate; DPA: diisopropyl adipate; MFTG: medium chain fatty acid triglyceride; PETA: polyester adipate.

The values in the monomer columns are the weight percentages of each monomer with respect to 100 as the total dry copolymer weight. The values in the plasticizer column are the weight percentages of each plasticizer with respect to 100 as the total weight of the pressure-sensitive adhesive layer.

[0061]

Example 11 Production of tape preparation for percutaneous absorption 11

A 36.2 g portion of pressure-sensitive adhesive 7, and
5 then 1.5 g of ketoprofen, were placed in a screw-cap bottle
and stirred for more than an hour in the bottle. A coating
tester (LTE-S, Wener Mathis AG) was used for coating and
drying of the solution onto a support (polyester film) to a
dried coating weight of 140 mg/10 cm², and then a liner
10 (silicon-treated polyester film) was used to cover it with
the silicon side contacting the pressure-sensitive to obtain
tape preparation for percutaneous absorption 11. The
ketoprofen content of the obtained preparation was 10 w/w%.

[0062]

15 Example 12 Production of tape preparation for percutaneous
absorption 12

A 35.69 g portion of pressure-sensitive adhesive 7, and
then 3.0 g of IPM and 1.5 g of ketoprofen, were placed in a
screw-cap bottle and stirred for more than an hour in the
20 bottle. A coating tester (LTE-S, Wener Mathis AG) was used
for coating and drying of the solution onto a support
(polyester film) to a dried coating weight of 140 mg/10 cm²,
and then a liner (silicon-treated polyester film) was used
to cover it with the silicon side contacting the pressure-
25 sensitive to obtain tape preparation for percutaneous
absorption 12. The ketoprofen content of the obtained
preparation was 10 w/w%.

[0063]

Examples 13-16 Production of tape preparations for percutaneous absorption 13-16

Tape preparations for percutaneous absorption 13-16 were each produced by the same method as Example 11 or Example 12, using pressure-sensitive adhesive 7, a drug and if necessary IPM plasticizer.

[0064]

Comparative Examples 6-9 Production of comparison tape preparations for percutaneous absorption 6-9

Comparison tape preparations for percutaneous absorption 6-9 were produced by the same method as in Example 12, using a specific drug and plasticizer, with a commercially available solvent-type acrylic pressure-sensitive adhesive for Comparative Examples 8 and 9 and addition of an isocyanate crosslinking agent for Comparative Examples 6 and 7

[0065]

The compatibility evaluation and tape adhesive and cohesive strength evaluation described in Test Example 1 were conducted using the tape preparations for percutaneous absorption 11-16 obtained in Examples 11-16, and the comparison tape preparations for percutaneous absorption 6-9. The tape preparations for percutaneous absorption according to the invention exhibited satisfactory adhesive and cohesive strength, while the comparison tape preparations for percutaneous absorption exhibited inferior adhesive and

cohesive strength. The results are shown in Table 3.

[0066]

Table 3 Compatibilities, adhesive strengths and cohesive strengths of medicinal tapes for percutaneous absorption

Example	Pressure-sensitive adhesive	Crosslinking agent (amount)	Plasticizer (amount)	Drug (amount)	Compatibility	Adhesive strength	Cohesive strength
11	Adhesive 7	-	-	ketoprofen 10	o	o	o
12	Adhesive 7	-	IPM 20	ketoprofen 10	o	o	o
13	Adhesive 7	-	-	indomethacin 10	o	o	o
14	Adhesive 7	-	IPM 20	indomethacin 10	o	o	o
15	Adhesive 7	-	-	tulobuterol 10	o	o	o
16	Adhesive 7	-	IPM 20	tulobuterol 10	o	o	o
Comp. Ex. 6	Nissetsu PE300	CK101 0.1	IPM 20	ketoprofen 10	o	-	x
Comp. Ex. 7	Nissetsu PE300	CK101 0.1	IPM 20	indomethacin 10	o	-	x
Comp. Ex. 8	Nissetsu PE300			tulobuterol 10	o	-	x
Comp. Ex. 9	Nissetsu PE300		IPM 20	tulobuterol 10	o	-	x

CK101: isocyanate crosslinking agent CK101 (Nippon Carbide Industries Co., Ltd.);

Nissetsu PE300: Solvent-type acrylic pressure-sensitive adhesive, Nissetsu PE300 (Nippon Carbide Industries Co., Ltd.);

IPM: isopropyl myristate.

The values for the crosslinking agents, plasticizers and drugs are weight percentages with respect to 100 as the total dry weight of the pressure-sensitive adhesive layer.

[0067]

Test Example 2 Drug release test

Each preparation was applied onto extracted skin of a Yucatan micropig (YMP) and allowed to stand under conditions of 32°C-60% RH. After 24 hours, the preparation was peeled off and the residual drug content of the preparation was measured by HPLC. The residual drug content was used to calculate the drug release rate (%) from the preparation. (drug content before application - residual drug content)/drug content before application x 100 = drug release rate (%)

[0068]

Test Example 3 Hairless mouse extracted skin permeability test

After placing 0.05 mol/L McIlvaine Buffer (pH 7.4) on the cutis side (receiver side) of the extracted skin in a vertical diffusion cell, the preparation was applied to the horny layer side. The receiver solution was sampled at different time points, and then an equivalent amount of 0.05 mol/L McIlvaine Buffer was added. The drug concentration of the sampling solution was measured by HPLC, and the flux, lag time and 24 hr cumulative permeation were calculated.

[0069]

Table 4 Drug release rates and skin permeabilities of medicinal tapes for percutaneous absorption

	Pressure-sensitive adhesive	Plasticizer (amount)	Drug (concentration)	Release rate (%)	Lag Time (hr)	FLUX ($\mu\text{g}/\text{cm}^2/\text{hr}$)	Cumulative permeation ($\mu\text{g}/\text{cm}^2/24 \text{ hr}$)
Example 15	Adhesive 7	-	tulobuterol 10	95.7 \pm 0.8	2.31 \pm 0.98	1.757 \pm 0.398	17.71 \pm 4.27
Example 16	Adhesive 7	IPM 20	tulobuterol 10	96.1 \pm 0.3	0.17 \pm 0.17	3.620 \pm 0.057	29.40 \pm 1.23
Comp. Ex. 8	Nissetsu PE-300	-	tulobuterol 10	88.9 \pm 0.2	5.14 \pm 1.93	0.335 \pm 0.133	3.30 \pm 1.12
Comp. Ex. 9	Nissetsu PE-300	IPM 20	tulobuterol 10	83.0 \pm 0.4	1.10 \pm 0.28	2.238 \pm 0.008	20.98 \pm 2.24

IPM: isopropyl myristate; Nissetsu PE300: Solvent-type acrylic pressure-sensitive adhesive Nissetsu PE300 (Nippon Carbide Industries Co., Ltd.).

The values for the plasticizer and drug are the weight percentages with respect to 100 as the total weight of the pressure-sensitive adhesive layer.

[0070]

A drug release test and skin permeability test were conducted for Test Examples 2 and 3, using the tape preparations for percutaneous absorption 15 and 16 of the examples and the tape preparations for percutaneous absorption 8 and 9 of the comparative examples. The results are shown in Table 4. The tape preparations for percutaneous absorption of the examples according to the invention had significantly superior drug release rates and skin permeabilities compared to the tape preparations for percutaneous absorption of the comparative examples.

[0071]

Test Example 4 Cumulative skin irritation test (rabbit)

Rabbits used for the test were shaved on the back with an electric razor up to the day prior to the test.

The preparation was applied onto the back of a rabbit or guinea pig, impermeable oiled paper was laid thereover, a nonwoven fabric pressure-sensitive adhesive bandage (MESHPORE, Nichiban) was attached firmly over it, and the entire application site was covered with gauze and then covered with a pressure-sensitive adhesive elastic bandage (ELASTOPORE, Nichiban). After 6 hours, the test preparation was removed and the site of application was lightly scraped with absorbent cotton wetted with lukewarm water and allowed to stand for 30 minutes, after which the site of application was observed. After observation was complete, the test preparation was applied at the same site and the same

procedure was repeated for 7 days. The application site was observed in the same manner at 48 and 72 hours after final removal of the preparation, and a rating was assigned based on the following evaluation scale of Draize et al.

5 [0072]

Evaluation scale of Draize et al.

A: Erythema and scab formation

No erythema: 0; Very mild erythema: 1; Apparent
erythema: 2; Medium to severe erythema: 3; Severe erythema
10 to slight scab formation: 4.

B: Edema formation

No edema: 0; Very mild edema: 1; Mild edema: 2;
Moderate edema (approximately 1 mm protrusions): 3; Severe
edema: 4.

15 [0073]

The 7-day cumulative skin irritation test described in Test Example 4 was conducted using a Japanese Pharmacopeia bandage and tapes 2-18 of the invention shown in Table 2, and the rabbit skin cumulative skin irritation scores were
20 determined. As a result, the score for tapes 2-18 using pressure-sensitive adhesives of the invention was 4.0 while the score for the Japanese Pharmacopeia bandage was 14.6, thus indicating that the pressure-sensitive adhesives of the invention are highly safe, with low irritation on rabbit
25 skin.

Table 5 Rabbit 7-day cumulative skin irritation test

	Cumulative irritation (7 days)
Japan Pharmacopeia bandage	14.6
Invention tapes 2-18	4.0

The average scores were calculated by the following formula.

The 7-day cumulative irritation represents the cumulative

5 total of the average scores from day 1 to day 9.

Average score = [(total of erythema scores) + (total of edema scores)]/5

Industrial Applicability

10 [0075]

In the process of heat drying, the nonaqueous pressure-sensitive adhesive of the invention forms a network structure by self-crosslinking of the acetoacetyl groups, so that large amounts of oily substances such as the

15 plasticizer can be included in the network structure. The pressure-sensitive adhesive of the invention uses no polyamine derivatives, isocyanate compounds, polyvalent metal chelate compounds or the like as crosslinking agents, and therefore since toxicity is not a concern and the skin
20 is not irritated, the adhesive is suitable for medical use. The medicinal tape preparation for percutaneous absorption of the invention is superior from the standpoint of adhesive strength, cohesive strength, safety, drug release property and percutaneous absorption.

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